RESEARCH NOTE

CHARACTERISTICS AND OUTCOMES OF HOSPITALIZED PATIENTS WITH INFLUENZA A(H1N1)pdm09 AT A TERTIARY CARE HOSPITAL, PESHAWAR, KHYBER PAKHTUNKHWA PROVINCE, PAKISTAN (2018 - 2019)

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Abstract. Swine-origin influenza A(H1N1)pdm09 virus first appeared in 2009 and has spread worldwide and is still circulating among the global population. Data were collected of demographic profile, preexisting medical conditions, clinical features, clinical laboratory data, duration of hospital stay, and outcome of patients (n = 39) with suspected or confirmed influenza A(H1N1)pdm09 infection admitted to Northwest General Hospital and Research Centre, Peshawar, Khyber Pakhtunkhwa Province, Pakistan from January 2018 to December 2019. Patients were 52 ± 16 (mean ± SD) years of age, with female:male ratio of 2:3. Clinical presentations were fever, shortness of breath, cough, chest pain, sore throat and body ache, with the most common comorbidity being hypertension (54%), followed by diabetes (28%) and then chronic kidney disease (8%). RT-quantitative PCR positivity was detected in 92% of the patients. Patients were treated with fever medication, fluid therapy, antiviral therapy, and oxygen support via non-invasive and invasive mechanical ventilation, with 77% survival rate. This study discloses a potentially deadly nature of the influenza A(H1N1) virus with a high mortality rate of individuals having comorbidities and secondary infections.

Keywords: comorbidity, influenza A(H1N1)pdm09 virus, mortality, Pakistan

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INTRODUCTION

Influenza-associated respiratory excess mortality rates (EMR)-contributing countries represent 57% of the global population, with an estimated mean annual influenza-associated EMR ranging from 0.1-6.4, 2.9-44.0 and 17.9-223.5 per 100,000 individuals for people <65, 65-74 years and >75 years of age, respectively (Iuliano *et al*, 2018). Influenza A and B viruses are the causes of seasonal flu epidemics. Influenza A viruses are classified into subtypes according to combinations of surface hemagglutinin (HA) and neuraminidase (NA); current subtypes circulating in humans are A(H1N1), A(H2N2), and A(H3N2), the former also known as A(H1N1)pdm09 as it caused the 2009 pandemic (only influenza type A viruses are known to have caused pandemics) and subsequently replaced seasonal influenza A(H1N1) virus that has been circulating prior to 2009 (Wu and Wilson, 2017). Influenza B viruses are divided into two lineages, B/Yamagata or B/Victoria (WHO, 2018).

Influenza type A virus possesses an ability to periodically change its antigenic structure (antigenic shift and drift) (Webster and Govorkova, 2014). Antigenic drift occurs more frequently during viral replication and commonly causes annual epidemics while antigenic shift rarely happens and occurs during an influenza pandemic. Incubation period of influenza type A virus is ~24-48 hours, followed by appearance of symptoms, such as rapid onset of fever, headache, fatigue, and muscle pain, which are associated with manifestations of respiratory tract complications, presenting as cough, sore throat and rhinitis (Caini *et al*, 2018; Kalish *et al*, 2019). A common and dangerous complication is bacterial pneumonia, which results in a high mortality rate, mainly attributed to refractory hypoxia (Nin *et al*, 2011).

Influenza A(H1N1) virus first appeared in Mexico during spring of 2009 and spread swiftly across the globe (Viasus *et al*, 2012). On 11 June 2009 a phase six pandemic alarm was declared

by the World Health Organization (WHO), suggesting the start of the 21st century influenza pandemic, and by the end of 2009 influenza outbreak has occurred in the majority of countries worldwide (Van Kerkhove *et al*, 2011). Influenza A(H1N1)pdm09 virus is still circulating globally, undergoing viral evolution and antigenic variability (Hsieh *et al*, 2018). During the pandemic, a total of 18,631 deaths were reported among the laboratory-confirmed cases, yielding a fatality rate of 2.9% with an estimated fatality rate of 0.02% among all infected individuals. A recent study estimated that between 123,000 and 203,000 people died during the pandemics, and 62-85% of these were under 65 years old (and often under 14 years old): these figures suggest that the mortality rate for the 2009 influenza pandemic was in fact 10 times higher than the mortality rate resulting from the laboratory-confirmed cases (Baldo, *et al*, 2016) and imposing an enormous economic burden involving both direct and indirect expenses in each affected country (Fu *et al*, 2019). A lag between presentations of symptoms and initiation of treatment was linked to unfavorable outcome (Zarychanski *et al*, 2010). However, longitudinal reviews/studies are required to arrive at an estimation of cases requiring extended hospitalization, progressing to respiratory failure and mortality (Lynfield *et al*, 2014).

In Pakistan, the earliest case of swine flu (influenza A(H1N1) virus), confirmed by laboratory testing, was detected on 10 August 2009, with subsequent occasional reported cases (Ishaque, 2010). An influenza A(H1N1) virus outbreak occurred from the winter of 2015 to February 2016 in Peshawar, Khyber Pakhtunkhwa Province, with 26 confirmed cases (Ijaz *et al*, 2017). However, a limited number of studies have been carried out in Pakistan regarding hospitalizations of infected patients, clinical manifestations, and outcomes.

Here, clinical manifestations and outcomes in influenza A(H1N1) virus-infected patients admitted to a hospital in Peshawar, Khyber Pakhtunkhwa from January 2018 to December 2019.

MATERIALS AND METHODS

Study site and recruitment of participants

Patients with suspected or confirmed influenza A(H1N1) virus infection attending the Department of Medicine, Northwest General Hospital and Research Centre (NWGH & RC), Peshawar, Khyber Pakhtunkhwa, Pakistan from January 2018 till December 2019 were recruited.

Research protocol was approved by the ethics committee, NWGH & RC (reference no. IRB-EB/NWSM/696/2020). Prior written consent was obtained from all participants.

Treatment and data collection

Participants enrolled were in-patients presenting respiratory symptoms and tested positive for the presence of influenza A(H1N1) virus in

respiratory specimens, (nasopharyngeal swab, nasal aspirate, or a combined nasopharyngeal swab with an oropharyngeal swab) using RT-quantitative PCR assay (CDC, 2009). Admission was in accordance to NWGH & RC policy and patients were treated in isolation rooms specific for suspected or confirmed influenza A(H1N1) virus infection. Blood samples for biochemical analysis were collected on the day of admission. Treatment included fever medication, fluid therapy, antiviral therapy, and oxygen supplementation via noninvasive and invasive mechanical ventilation.

A structured questionnaire was used to collect data on socio-demographic profile, underlying medical conditions, history of smoking, duration of hospital stay, clinical laboratory data, treatment, and outcome. Clinical manifestations of participants were followed until discharge from the hospital or (in the worst-case scenario) progression to death.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as percentage and frequency. Comparison of continuous variables was performed using an independent Student's t-test and that of categorical variables using a chi-square test. A two-sided p-value <0.05 is considered statistically significant. Calculations were carried out using the Statistical Package for the Social Sciences (SPSS), version 23 (SPSS, Chicago, IL).

RESULTS

Patients (n = 39) with suspected influenza A(H1N1) virus infection admitted at NWGH & RC, Peshawar from January 2018 till December 2019 had a mean (± SD) age of 52 (± 16) years old, with a male:female ratio of 2:3, and presented with cough (n = 39, 100%), shortness of breath (n = 37, 95%), fever (n = 36, 92%), body ache pain (n = 31, 79%), chest pain (n = 31, 79%), and sore throat (n = 31, 79%). Subsequent test for influenza A(H1N1) virus in respiratory specimens, (nasopharyngeal swab, nasal aspirate, or a combined nasopharyngeal swab with an oropharyngeal swab) using molecular assay (PCR) revealed 92% (n = 36) positivity.

Blood laboratory findings showed lower pO2 and pCO2 levels, and higher values of C-reactive protein, plasma troponin I and erythrocyte sedimentation rate than hospital normal range, while other parameters were within hospital normal range (Table 1).

The most frequent comorbidity was hypertension (n = 21, 54%), followed by diabetes (n = 11, 28%) and chronic kidney disease (n = 3, 8%). Only 3 (8%) patients were current smokers. Almost all patients receive a treatment of an antipyretics, anti-viral, i/v fluids, supplemental oxygen who needs it and invasive ventilation and non-invasive mechanical ventilation for appropriate patients. Thirty (77%) were discharged after a hospital stay of 7 ± 4 days but nine patients failed to respond to

Table 1

Laboratory investigations of suspected and confirmed cases of influenza A(H1N1) virus infection among patients admitted at the Department of Medicine, Northwest General Hospital and Research Centre, Peshawar, Khyber Pakhtunkhwa Province, Pakistan (January 2018 - December 2019)

Parameter	Mean (SD) (n = 39)	Hospital normal ranges
Hemoglobin, g/dl	13 (2)	12.5 - 16.5
White blood cell count, $\times 10^3$ cells/ml	9 (5)	4.0 - 11
Platelets, 10^9/l	216 (104)	150 - 450
pH	7.4 (0.1)	7.35 – 7.45
pO_2, mmHg	64 (19)	80 - 100
pCO_2, mmHg	34 (9)	35 - 45
C-reactive protein, mg/dl	13 (9)	<0.5
Erythrocyte sedimentation rate, mm/hour	46 (26)	0 - 20
Serum creatinine, mg/dl	1.1 (0.9)	0.6 -1.2
Blood urea, mg/dl	46 (37)	15- 40
Serum alanine transaminase, U/l	39 (24)	7 - 55
Serum albumin, g/dl	3.1 (0.7)	3.4 - 5.4
Plasma troponin I, ng/l	2,412 (9,903)	<40

g/dl: grams per deciliter; ml: milliliter; l: liter; mg/dl: milligram per deciliter; mmHg: millimeters of Mercury; mm/hour: millimeter per hour; ng/l: nanogram per liter; U/l: Units per liter

treatment. Factors significantly associated with mortality were (in decreasing order of relative significance) secondary infection, a requirement of ionotropic support, oxygen ventilation, renal failure, and septic shock (Table 2).

DISCUSSION

Our study of in-patients with influenza A(H1N) virus infection at a hospital in Peshawar, Khyber Pakhtunkhwa, Pakistan over 3 months reveals mortality (although constituting less than 25% of the patients) is significantly associated with secondary infection, requirement of ionotropic support, oxygen ventilation, renal failure, and septic shock.

Table 2

Clinical features of recovered and non-surviving of influenza A(H1N1) virus infection among patients admitted at the Department of Medicine, Northwest General Hospital and Research Centre, Peshawar, Khyber Pakhtunkhwa Province, Pakistan (January 2018 - December 2019).

Characteristic	Recovered Number (%) (n = 30)	Non-surviving Number (%) (n = 9)	p-value*
Age, years (SD)	52 (16)	51 (17)	0.80
Gender			0.60
Male	13 (43)	4 (44)	
Female	17 (57)	5 (56)	
Smoking status			0.50
Smoker	2 (7)	1 (11)	
Non-smoker	28 (93)	8 (89)	
Length of hospital stay, days (SD)	7 (4)	7 (5)	0.60
Duration of symptoms, days (SD)	7 (3)	9 (5)	0.20
Respiratory failure	21 (70)	9 (100)	0.10
Renal failure	6 (20)	6 (67)	0.02
Ionotropic support	3 (10)	8 (89)	<0.001
Secondary infection	19 (63)	9 (100)	0.03
Septic shock	3 (10)	9 (100)	<0.001
Ventilator support	11 (37)	9 (100)	0.001
Oxygen support	22 (73)	7 (78)	0.60

*Significant at p <0.05

SD: standard deviation

Ijaz *et al* (2017) in Peshawar, noted length of hospital stay is significantly longer among patients recovering from influenza A infection, but this was not evident in our study and that by Kumar *et al* (2012) in Bangalore, India. A longer hospital stay places patients at risk of acquiring nosocomial infections.

Other studies in Pakistan have observed mortality among influenza A patients is associated with oxygen ventilation support (Ijaz *et al*, 2017; Tapaira *et al*, 2018) as well as in China (Cui *et al*, 2010).

Fajardo-Dolci *et al* (2010) described comorbidities among influenza A(H1N1) patients at Mexico city were predominantly metabolic syndromes (40%), followed by cardiovascular diseases (21%), hypertension (20%) and diabetes mellitus (20%), in line with the present study.

The study suffers from two major limitations. Firstly, this was cross-sectional rather than prospective and so may be susceptible to confounding effects ("reverse causation") (Rehman *et al*, 2021; Dhingra *et al*, 2017). Secondly, the sample size was small and limited to a single hospital, thereby unable to generalize the findings across the city, l*et al*one the province. Future large-scale, multi-center prospective studies are needed to understand the clinical spectrum of influenza A (H1N1) pdm09.

In conclusion, the study has highlighted several factors contributing to mortality among influenza A(H1N1) pdm09 patients in a northwestern region of Pakistan, which should be of assistance to physicians in making evidence-based decisions on appropriate management of patients and reduce the mortality rate among patients with a potentially deadly influenza A infection.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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